REMARKS

Applicants thank the Examiner for his review of the instant application. For the reasons stated below, the rejections of the presently pending claims are respectfully traversed. Claims 6-7, 9 and 11-17 remain present for examination.

Rejection Under 35 U.S.C. §101

The PTO has maintained the rejection of the pending claims under 35 U.S.C. § 101 as lacking utility. The PTO states that "[t]here are no data presented as to whether the protein (SEQ ID NO:48, also called PRO994) is differentially expressed in any tumor, nor is there evidence of the utility of the antibody for diagnosis or treatment of any disease." *Office Action* at 2.

For the reasons set forth below, Applicants respectfully disagree.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the Examiner has not met the PTO's burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. However, even if the Examiner has met the PTO's initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is **more likely than not** that a person of skill in the art would be convinced, **to a reasonable probability,** that the asserted utility is true. As stated previously, Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. **The standard is not absolute certainty.**

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

Applicants remind the PTO that the asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO994 polypeptide is expressed at least two-fold higher in normal stomach tissue and rectal tumor tissue as compared to stomach tumor tissue or normal rectal tissue, respectively;

2. Applicants assert that it is well-established in the art that a change in the level of mRNA for a particular protein, *e.g.* an increase or decrease, generally leads to a corresponding change in the level of the encoded protein, *e.g.* an increase or decrease; and

3. Given the differential expression of the PRO994 mRNA in stomach and rectal tumors compared to normal stomach and rectal tissue, respectively, it is more likely than not that the PRO994 polypeptide is also differentially expressed in stomach and rectal tumors compared to normal stomach and rectal tissue, respectively, making the claimed polypeptides useful as diagnostic tools, alone or in combination with other diagnostic tools.

Applicants understand the PTO to be making the following arguments in response to Applicants' asserted utility:

The PTO continues to rely on Hu *et al.*, Chen *et al.*, and Tokunaga, as well as newly produced references by Nagaraja *et al.* (Oncogene, (2006) 25:2328-38), Waghray *et al.* (Proteomics, (2001) 1:1327-38) and Sagynaliev *et al.* (Proteomics, (2005) 5:3066-78) to support its position that changes in the level of mRNA do not necessarily reflect changes in protein expression levels. The PTO argues that the Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* references support the idea that "increases in mRNA and protein samples are not correlated." *Office Action* at 6.

The PTO also states that Applicants previously submitted references are not persuasive with regard to the instant application and the question of whether changes in mRNA levels correlate with changes in protein levels. According to the PTO, Exhibits 2-13, with the exception of Ornstoft *et al.* (Mol. Cell. Proteomics, (2002) 1:37-45), are only directed towards a single gene or a small number of genes. Thus, in regard to the correlation between changes in mRNA levels and changes in protein levels, these exhibits "are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined, specifically, Nagaraja (2006), Waghray (2001) and Sagynaliev (2006)...." *Office Action* at 6. The PTO contends that the Ornstoft *et al.* reference, which compares the mRNA and protein levels of about 40 well-resolved, focused and abundant proteins with known chromosomal locations, has no relevance to the instant application because Applicants have not provided any evidence that PRO994 is a well-focused abundant protein with a known chromosomal location.

Applicant's maintain that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

The PTO has Concluded that the data in Example 18 are Sufficient to Establish the Utility of the Claimed Invention

As an initial matter, Applicants point out that in other applications filed by Applicants that rely *on data from the exact same disclosure, Example 18*, and in which Applicants have submitted *substantially the same references* in support of their asserted utility, the PTO has concluded that: "[b]ased on the totality of evidence of record, **one of skill in the art would find it more likely than not that an increase in message as measured by RTPCR would be predictive of an increase in protein expression levels,** absent evidence to the contrary. Therefore, the data presented in Example 18, which demonstrates differential expression of nucleic acids encoding PRO1180, also supports a conclusion of differential expression of PRO1180 polypeptide. Therefore, one of ordinary skill in the art would be able to use the PRO1180 polypeptide diagnostically for distinguishing normal kidney and rectal tumor tissues compared to kidney tumor and normal rectal tissue, as asserted by Applicant." See *Examiners Reasons for Allowance* in pending Application No. 10/063,529. See also *Examiners Reasons for Allowance* in Application No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583, all of which conclude that the data presented in Example 18, which demonstrate differential expression of the nucleic acids encoding certain PRO polypeptides, also support a conclusion of differential expression of the PRO polypeptides, making the claimed PRO polypeptides and antibodies that bind the PRO polypeptides useful for diagnostic purposes.

Applicants therefore request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and Applicants numerous cited references, as was done in the other applications referenced above.

The Previously Cited References Provide Evidence that Changes in mRNA Levels are Correlated with Changes in Protein Levels

Applicants incorporate by reference their previously submitted arguments in regard to Hu *et al.*, Chen *et al.*, and Tokunaga and will not reiterate those arguments here. However,

Applicants will once again explain why the PTO's reliance on Hu is misplaced. Hu bases his conclusions on data generated from high throughput microarrays:

> In any microarray experiment, thousands of genes may demonstrate statistically significant expression changes, but only a fraction of these may be relevant to the study. *Hu* at 405, left column, first paragraph (emphasis added).

As Applicants previously pointed out, Applicants are relying on a more accurate and reliable method of assessing changes in mRNA level, namely quantitative PCR analysis. Applicants submitted a reference by Kuo *et al.*, (Proteomics 5(4):894-906 (2005)), in which the authors state that PCR is a "more reliable and sensitive" than microarray technology. *Kuo et al.* at Abstract (emphasis added). Thus, even if accurate, Hu's statements regarding microarray studies are not relevant to the instant application which does not rely on microarray data.

In response, the PTO argues that "[t]he source of Hu's data are not particularly relevant to the validity and applicability to the instant case," and that Kuo is not persuasive because Kuo *et al.* "clearly teach that the amount of mRNA and protein determined to be in a sample is highly technique-dependent." *Office Action* at 4.

Applicants maintain that Kuo supports their assertion that Applicants' PCR data are more accurate and reliable than the microarray data relied on by Hu. Because PCR is more accurate and reliable than microarrays, conclusions regarding the relevance of mRNA transcript changes based on microarray data, such as those set forth in Hu, are not applicable to data generated using the more reliable method. Kuo supports this assertion because it is evidence that one of skill in the art would regard PCR as a more accurate and reliable method of assessing changes in mRNA.

In addition, as pointed out previously, in contrast to the analyses performed by Tokunaga where the presence or absence of CK18 mRNA or the specific amount of CK18 mRNA is being assessed, in the experiments described in Example 18 of the present specification the relative levels of mRNA in normal tissue and tumor tissue are compared. In such situations, where one is looking for *relative differences* rather than the presence or absence of an amplification product or the specific amount of an amplification product, qualitative analyses are sufficient. Applicants maintain that the semi-quantitative analysis described in Example 18 provides a reliable indication of the differential expression of the PRO994 mRNA.

The PTO's Newly Cited References (Nagaraja et al., Waghray et al. and *Sagynaliev et al.) Do Not Support the Conclusion that Changes in mRNA Expression Do Not Result in Changes in Protein Expression*

Applicants continue to assert that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; given Applicants' evidence of differential expression of the mRNA for the PRO994 polypeptide in stomach and rectal tumors, it is more likely than not that the PRO994 polypeptide is also differentially expressed; and proteins differentially expressed in certain tumors, and antibodies that bind such proteins, have utility as diagnostic tools.

In response to Applicants' assertion, the PTO cites new references by Nagaraja *et al.* (Oncogene, (2006) 25:2328-38), Waghray *et al.* (Proteomics, (2001) 1:1327-38) and Sagynaliev *et al.* (Proteomics, (2005) 5:3066-78) as support for the argument that "increases in mRNA and protein samples are not correlated." *Office Action* at 6.

The PTO argues that in Nagaraja *et al.*, researchers observed that there were fewer changes observed in protein abundance as compared to transcript abundance between various malignant and normal breast cell lines and that "[t]he comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*". The PTO sees these observations as support for its contention that mRNA levels are not predictive of protein levels, even when considering the effect of changes in mRNA levels on protein levels. However, a careful examination of Nagaraja *et al.* shows that the reference does not contain evidence that supports the PTO's position.

Nagajara and colleagues analyzed the transcriptosomes and proteosomes of normal and malignant breast cell lines. In the studies of the transcriptosomes of these cell lines, the gene chips used in the microarray analysis could detect 18,400 gene or gene variants. Nagajara *et al.* reported over 1000 genes that had a two-fold or greater differential level of expression between the various cell lines studied. The researchers distingushed between differentially expressed transcripts that were upregulated and those that were downregulated, comparing the normal cell line to the malignant ones and the malignant ones to each other (Figure 5, pg. 2332).

However, in their proteosome studies, the researchers used techniques that were far less sensitive and only able to detect a small number of proteins: "Typically, > 300 protein spots could be visualized in silver-stained gels, and there were far fewer protein spots in gels that were stained with Coomassie blue" (pg. 2332). While the gene chips used by the researchers in their transcriptosome work could detect 18,400 gene and gene variant transcripts, the proteosome analysis techniques used by the researchers could only detect a much smaller number of proteins. Evidently, the protein analysis techniques used were not sensitive enough to detect any but the most abundant proteins. As a result, the total number of proteins detected in the most sensitive protein gel used ("> 300") was only 1/3 of the total number of transcripts found to be differentially expressed and only about 17% of the total number of transcripts that could be identified by microarray analysis. The proteins detected do not represent a random, representative sample of proteins from the cells; instead, they actually represent a sample of only the most highly expressed and abundant proteins. Additionally, the proteins selected for identification from the gels were only those proteins that were either *upregulated* or solely detected in the malignant cell lines, as compared to the normal cell line. Proteins that were downregulated in the malignant cell lines, only expressed in the normal cell line or differentially expressed between the malignant cell lines were not studied in the proteosome analysis.

Nagaraja's experimental methods and results are not contrary to Applicants' assertions. Nagaraja's "comprehensive study" looked at no more than 25 mRNA/protein pairs. The total number of proteins detected in the most sensitive protein gel was about 300, which was less than 2% of the total number of transcripts that were identified by Nagaraja's microarray analysis. The proteins selected by Nagaraja as differentially expressed were only those proteins that were solely detected in the malignant cell lines, as compared to the normal cell line. Proteins that were detected in the normal cell line, whether upregulated, downregulated, or absent in the malignant cell lines relative to the normal cells lines, were omitted from the proteosome analysis. In the end, only 25 proteins were examined, which is about 2.5% of the number of differentially expressed transcripts detected. Even then, Nagaraja does not indicate whether or not corresponding transcripts were detected for each of these 25 proteins. Thus, Nagaraja looked at 25 or fewer mRNA/protein pairs.

Nagaraja's experimental methods and results do not teach even a single instance in which differentially expressed mRNA did not have a similarly differentially expressed encoded polypeptide. Nagaraja may very well have detected some differentially expressed proteins that were not associated with differentially expressed mRNAs. Such a result is not contrary to Applicants' assertions that differential mRNA levels typically correspond to differential levels of the encoded polypeptide. Evidence in Nagaraja of differentially expressed protein when mRNA is not differentially expressed cannot lead to the conclusion that differential mRNA levels fail to lead to corresponding differential protein levels. Accordingly, these results cannot be construed as contrary to Applicants' assertions.

Due to the difference between the techniques used and the strategies employed by the researchers in this study, the data from the transcriptosome and proteosome studies cannot be reliably compared to one another. The transcriptosome studies examined 18,400 transcripts and variants and uncovered thousands of differentially expressed transcripts, both upregulated and downregulated. The proteosome studies only detected around 300 of the most abundant proteins in the cell lines. The researchers only selected proteins that were upregulated or solely expressed in malignant cells for study. Thus, genes expressed at a relatively low rate or gene products that are relatively less abundant were included in the transcriptosome study but excluded from the proteosome study. Additionally, different criteria were used for defining altered expression of transcripts than were used to select proteins for identification. The criteria for picking a protein for study (only those upregulated by two-fold or greater, or solely expressed, in malignant cells) was narrower than the criteria for examining differentially expressed transcripts (any transcript with a two-fold or greater upregulation or downregulation between any combination of two of the three cell lines examined). Thus, the population of genes examined in the proteosome experiments represents a small, non-random subset of the population examined in the transcriptosome experiment, both in terms of the total population of transcripts or gene products uncovered by the experiments and in terms of those particular transcripts or gene products that were identified as altered in expression. Because the genes analyzed in the proteosome experiments represent neither a similar set nor a representative, randomly selected subset of the genes analyzed in the transcriptosome experiments, no valid conclusions can be drawn by comparing the results from the two types of experiments to one another.

The PTO cites several sentences from Nagaraja *et al.* in support of its argument. Specifically, the PTO cites:

> "...the proteomic profiles indicated altered abundance of few proteins as compared to transcript profiles...";
>
> "The comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*"; and
>
> "As dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles."

However, as the above analysis of experimental techniques and design reveals, transcriptosome and proteosome study data cannot be compared to each other to draw conclusions about the relationship between mRNA levels and protein levels. This is due to a wide difference in technique sensitivity, which lead to the examination of drastically different portions of the total gene transcript or product populations, and an incompatible difference in the definition of altered expression for transcripts and proteins. Nagajara *et al.* found that the proteomic profiles had fewer proteins with an altered abundance as compared to the transcriptosome profiles and that the same genes with altered expression patterns were not always found in both proteomic and transcriptosomic profiles. However, from the observations made during analysis of the results of transcriptosome and proteosome research, Nagajara *et al.* drew no conclusions as to the relationship between mRNA levels and protein levels. All comments made by the authors are entirely consistent with conclusions of Sagynaliev, discussed *infra*: that there is a significant need to standardize the scientific methods of collecting, storing, retrieving and analyzing samples, as well as the querying of genetic expression data obtained through a variety of techniques. By pointing out the differences between the proteosome and transcriptosome studies, the authors were not implying that there was doubt about the relationship between mRNA levels and protein levels. Rather, they were pointing out the unreliability of any conclusions that could be drawn from comparisons between studies of differential transcriptosomes and studies of differential proteosomes.

Regarding the third statement relied upon by the PTO, the conclusions of Nagaraja *et al.* about *post-transcriptional* regulation are based on studies of a cell line that was genetically engineered in the laboratory to eliminate particular transcripts through the use of anti-sense

sequence technology. In these experiments, the authors deliberately reduced certain particular transcripts and then looked at the effects on cell cultures and proteosomes at one time point (when cultures were 70-80% confluent). As explained in greater detail under Waghray *et al. infra*, sudden changes and manipulations of transcript profiles can lead to wildly fluctuating levels of gene product within cells. Additionally, the amount of time that is needed to see the difference in gene product levels caused by changes and manipulations of transcript levels can vary widely from gene to gene, from hours to multiple days. Thus, examination of only one timepoint is insufficient to draw conclusions about the effects of dynamic changes and manipulations of transcript levels on protein abundance and is not relevant to the correlation between steady-state levels of mRNA and gene products. Furthermore, the authors are not certain about how the introduction of the antisense constructs is actually working to reduce the presence of the particular transcripts in question: "the antisense constructs... *appeared* to work as siRNAs..." (pg. 2335, emphasis added). In any case, laboratory data from cells genetically manipulated with non-native, unnaturally occurring sequences, which were packaged into expression vectors with foreign sequence elements and produced effects from uncertain subcellular mechanisms, has no relevance to Applicants' instant invention.

The PTO cites particular observations made in Waghray *et al.* to support its argument that mRNA levels are not necessarily predictive of protein levels, even when there is a change in mRNA levels. Waghray *et al.* looked at transcriptosomal and proteosomal changes in an androgen-sensitive prostate cancer cell line after the cells were treated with dihydrotestosterone (DHT). Out of 16,570 genes, the authors found 351 transcripts that were differentially expressed in the stimulated cells. The authors also identified 44 proteins, out of 1031 spots on protein gels, that were upregulated or downregulated in stimulated cells. Hence, Waghray *et al.* found that over 4% (44/1031) of the proteins isolated from the cells were differentially expressed while only 2% (352/16,570) of the transcripts were differentially expressed.

The PTO posits that if changes in protein generally reflected mRNA changes, one would only expect to see 2% of the proteins differentially expressed, i.e. 22 out of 1031 proteins, instead of the observed 44 proteins. However, Applicants make no assertion that differential protein levels always are accompanied by differential mRNA levels. The possibility that additional factors beyond differential mRNA levels also can lead to differential protein levels

does not imply that differentially expressed mRNA do not typically have a corresponding differentially expressed encoded polypeptide.

The PTO's conclusion requires that the set of 1,031 proteins found in the protein gels be a proportional, representative, randomized subset of the 16,570 genes found in the analysis of the transcripts. It is clear that the 1031 proteins found represent only a small subset of the 16,570 transcripts examined. The authors stated that "[a] relatively small set of genes could be analyzed at the protein level, largely due to the limited sensitivity of 2-D PAGE" (pg. 1337, emphasis added). Thus, similar to the results of Nagaraja *et al.* discussed *supra*, proteins found through the use of protein gels represent only the most abundant proteins of the cell, whereas the transcripts identified included transcripts of many proteins not abundant enough to be found via protein gels. Because the set of proteins identified do not represent a randomized subset of the transcripts identified, one cannot draw conclusions regarding the general relationship between changes in mRNA levels and changes in protein levels based on a comparison of these data.

The PTO also cites an additional statement by Waghray *et al.* in support of its argument that mRNA levels are not necessarily predictive of protein levels, even when there is a change in mRNA levels. Waghray *et al.* found that corresponding SAGE (sequence analysis) data were available for a number of the proteins identified as differentially expressed and stated that "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level (Table 4)." The PTO concludes from this statement that the data presented by Waghray *et al.* support its argument against a correlation between mRNA levels and protein levels.

However, further analysis of the data collected in these experiments shows that such a conclusion cannot be drawn from the data. The experiments of Waghray *et al.* that produced the data shown in Table 4 involve hormonally stimulating cells for 24 hours; determining mRNA levels in the cells; and, 48 hours after determining mRNA levels, determining protein levels, for specific mRNA/protein product pairs. The authors measured mRNA levels twice, before stimulating with DHT and after stimulating with DHT for 24 hours (24 hours post-treatment). They also measured protein concentrations twice, before stimulating with DHT and at 72 hours post-treatment. The second measurement of protein levels therefore occurred 48 hours after DHT was removed from the culture media. Thus, the experiment involved creating a dynamic

and changing environment for cells and the measurement of the effects of this changing environment at only one timepoint. Additionally, the timepoints used for measuring the effects on mRNA levels and protein levels were 48 hours apart.

Examining the two timepoints for particular genes, the authors stated that there was not appreciable concordant change at the RNA level for most of the proteins whose concentrations were affected by DHT treatment. However, the differential expression of mRNA at 24 hours and of protein at 72 hours does not reveal the complete picture of the effects of DHT treatment on the cells. The authors noted that the dynamic conditions of the experiments created fluctuating levels of both mRNA and protein over time (pg. 1337). They decided to examine the kinetics of mRNA and protein levels for two proteins affected by DHT treatment, PSA and clusterin (Fig. 1C on pg. 1334). PSA is known to be an androgen-regulated gene and the authors had been surprised to see only a 1.7 fold induction of PSA transcripts by DHT treatment at the 24 hour timepoint. But through the kinetic experiment, they saw that induction of PSA began between 4 and 6 hours post-treatment and they detected a 5 to 10 fold induction of PSA at 6 to 8 hours post-treatment. PSA mRNA levels subsequently declined, so that by the time samples were taken for SAGE analysis at 24 hours post-treatment, only a 1.7 fold induction was seen. The results of the clusterin kinetic experiment show an even greater effect of DHT treatment on induction and greater fluctuation ranges. Clusterin mRNA induction began sooner than PSA induction (only 0.5 to 1 hour post-treatment), declined between 6-12 hours post-treatment, and at the 24 hour timepoint clusterin mRNA levels had declined to a lower level than the untreated control cells. Thus, while clusterin mRNA was initially induced to much higher than steady-state levels by DHT treatment, by the time the researchers quantified the levels of clusterin mRNA with SAGE at the 24 hour timepoint, clusterin mRNA levels had fallen *below* the levels measured pre-treatment. Due the dynamic nature of these stimulation experiments, it is clear that the observed effect of DHT treatment on the mRNA level of an affected gene will depend on *when* the observation is made. For example, with clusterin, one could observe a large induction of transcription (1-6 hours post-treatment), no change in mRNA levels (some point between 12 and 24 hours post-treatment), or a reduction *below untreated levels* of mRNA (24 hours post-treatment), all depending on the particular timepoint chosen for the collection of an RNA sample from treated cells. Because of these fluctuations of mRNA levels over time, the data from Table

4 have no relevance to the relationship between steady-state levels of mRNA and protein for a particular gene and cannot inform us as to the general relationship between mRNA levels and protein levels. This is especially true since the authors did not perform kinetic experiments on proteins affected by DHT treatment; it is unknown whether reduced levels of expression seen for some proteins in the table represent a persistent suppression of protein expression over a 72 hour period or merely a reduced level at just the 72 hour timepoint. Thus, the data from Table 4, upon which the authors base their observation about the concordance of mRNA and protein levels, actually provide no insight into the relationship between mRNA levels and protein levels in a dynamic experiment with stimulated cells, let alone for cells in a steady-state environment.

The PTO has cited the observations of Waghray *et al.* regarding their experiments on stimulated cells in support of its argument that mRNA levels are not necessarily predictive of protein levels, even when there are changes in the mRNA level. But because of the differences in transcript and protein detection efficiency and the dynamic nature of the stimulation experiments, no correlations between transcript and protein levels can be accurately drawn from the data presented. The conclusions of the authors have no relevance to and do not support the PTO's argument.

Waghray presents no more than 2 discernably differentially expressed mRNAs for which polypeptide levels were not similarly differential. However, based on Waghray's arbitrarily selected timepoints for measurement, there is no way to conclude that these 2 instances accurately reflect the relationship between mRNA and protein levels in the cell. As such, Waghray provides little or no basis to doubt Applicants' asserted utility.

The PTO also cites the work of Sagynaliev *et al.* to support its argument that mRNA levels are not predictive of protein levels, even when considering changes in mRNA levels. The Sagynaliev *et al.* reference is a review of scientific papers regarding gene expression in colorectal cancer (CRC) and describes an attempt by the writers to create a "data warehouse" combining the results of multiple researchers and laboratories into one database. The authors present statistics about how many genes have been found to be differentially expressed at the mRNA level versus at the protein level in CRC studies. The PTO points to these statistics as evidence of the discordance between mRNA and protein levels, noting that while 982 genes were found to be

differentially expressed in human CRC by genome-wide transcriptomics technologies, only 177 have been confirmed using proteomics technologies.

The work of Sagynaliev *et al.*, however, does not support the PTO's argument. In their conclusions, the authors are not suggesting that mRNA levels, changing or otherwise, are not predictive of protein levels. Instead, they see the disagreement between different studies, laboratories and experimental techniques as evidence that there is a great need for standardization in this research field: "Thus, the development of standardized processes for collecting samples, storing, retrieving, and querying gene expression data obtained with different technologies is of central importance in translational research" (pg. 3066).

Far from supporting the PTO's argument, the research of Sagynaliev *et al.* actually provides a list of problems with the research in the field which serve to reduce the reproducability of the experiments and thus make conclusions drawn from comparison of experimental results less reliable. Three of the problems listed by the authors serve to undermine the PTO's use of the data discussed *infra* in support of their argument. First, multiple factors can affect the outcome of a microarray experiment used to analyze a transcriptosome, including technical, instrumental, computational and interpretative factors. The authors found that when comparing different microarray experiments on CRC samples, only four of 185 genes selected behaved consistently on three array platforms and the agreement on the results from two brands of microarray was only about 30% (pg. 3077). Second, in proteomic studies, protein gels have well-known technological limitations, so that even under well-defined experimental conditions, 2-D PAGE analysis is "hampered by a significant variability" (pg. 3077). Third, because of "small sample size (number of patients), large number of variables examined at once, and absence of double or triple experiments (arrays and gels are expensive and samples are rare), statistical analysis is often *not valid*" (pg. 3077, emphasis added). Thus, reproducibility between transcriptosome analysis experiments or between proteosome analysis experiments is hampered by both the lack of technical standardization and the inherent variability of microarray and protein gel technologies. If the reproducibility of experimental results within particular areas of research is questionable, it is unlikely that conclusions drawn by comparing experiments between these research areas (e.g., examining *different* molecular populations) would be valid.

Furthermore, Sagynaliev provides no basis to conclude that differential mRNA levels are not typically reflected by differential levels of the encoded polypeptide. Sagynaliev reports and discusses consideration for assembling results generated from different methodologies. Sagynaliev's assembled data are not directed to the question of how differential mRNA levels influence polypeptide levels. Sagynaliev does not provide a single example in which differential mRNA levels for a particular gene were accompanied by unchanged, or oppositely differential, protein levels. Accordingly, Sagynaliev's findings cannot lead one to conclude that based on the assembled published data on CRC, differential mRNA levels do not lead to corresponding differential levels of the encoded polypeptide.

The PTO cites the studies of Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* as allegedly supporting the contention that differential mRNA levels are not typically accompanied by corresponding differential protein levels. However, Nagaraja *et al.* and Sagynaliev *et al.* do not report findings contrary to Applicants asserted utility. There is not even a single example in Nagaraja *et al.* or Sagynaliev *et al.* which shows that for a particular differentially expressed mRNA, polypeptide levels were not similarly differentially expressed. The "comprehensive study" of Waghray *et al.* reports 2 instances of discernably differentially expressed mRNAs in which the differential mRNA levels were not accompanied by similarly differential protein levels. However, the probative value of these 2 instances is questionable in view of the arbitrary time points selected for measuring dynamic mRNA and protein levels. In conclusion, the whole of the teachings of Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* provide little or no evidence that would lead one skilled in the art to doubt Applicants' asserted utility.

Previously Submitted Exhibits 2-13, including Orntoft et al., Are Relevant to the PTO's Argument Against Allowance of the Claims

Applicants previously submitted Exhibits 2-13, comprising 81 references, in support of their argument for the correlation between mRNA levels and protein levels. The PTO states that these references are all directed to a single gene or a small number of genes, with the exception of Orntoft *et al.* The PTO cites the studies of Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* in response. The PTO states that it considers these studies to be more relevant than Applicant's numerous references because they are more comprehensive, examining significantly larger numbers of transcripts and proteins. Applicants respectfully disagree.

For the reasons cited above, the references of Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* cannot be reliably used to draw conclusions about the relationship between mRNA and protein levels. Because of the problems cited above, inferences about the relationship between mRNA and protein levels cannot be accurately drawn by comparing large scale transcriptosomic and proteosomic studies. By examining individually a large number of single genes or small groups of genes, the Exhibits submitted by Applicants provide evidence of the Applicants' contention that mRNA levels and protein levels are correlated.

The PTO concedes that the Orntoft *et al.* reference examines more than just a small group of genes and that a significant correlation exists for mRNA and protein levels for the 40 genes examined. But because the proteins examined by Orntoft *et al.* are well-resolved and focused abundant proteins with known chromosomal locations, the PTO contends that the data are not applicable to the PRO994 gene and peptide, since Applicants have not provided any data suggesting that the PRO994 protein is well-focused and abundant or that the PRO994 gene's chromosomal location is known. Applicants respectfully disagree.

Orntoft *et al.* examined differences in the genetic changes that underlie invasive versus non-invasive bladder cancer. The authors stated in the abstract of their paper that "[b]ecause most proteins resolved by two-dimensional gels are unknown it was only possible to compare mRNA and protein alterations in relatively few cases of well focused abundant proteins" (Abstract). Hence, the authors' choice to examine well-focused and abundant proteins was due to the limitations inherent in protein gel technology to resolve and identify proteins. These limitations mean that researchers can only use 2D-PAGE to accurately identify and quantify the

proteins that are the most abundant and well-resolved by the protein gel. The authors did not determine that the correlation between mRNA and protein levels does not exist for less focused or less abundant proteins. They drew no conclusions about less focused or less abundant proteins because such proteins could not be reliably identified or quantified with 2-D protein gel technology. The PTO provides absolutely no evidence that any correlative relationship between mRNA levels and protein levels would be dependent upon the abundance of a protein, the ability of 2D-PAGE to resolve a protein, or whether the protein's chromosomal location could be determined with present technology. Thus, Applicants contend that the Orntoft *et al.* reference is indeed relevant and that it provides evidence refuting the PTO's argument against the correlation of mRNA and protein levels.

Applicants have shown above that the findings of Nagaraja *et al.*, Waghray *et al.* and Sagynaliev *et al.* cannot be relied upon to draw conclusions about the relationship between mRNA and protein levels. The numerous references provided by Applicant, including Orntoft *et al.*, however, provide strong evidence supporting the Applicants' position.

In addition, Applicants have previously submitted the Polakis Declaration in support of their position that in general, changes in mRNA levels correlate with changes in protein levels. Applicants submit herewith as Exhibit 1 a second Declaration by Dr. Polakis (Polakis II) that presents evidentiary data in Exhibit B. Exhibit B of the Declaration identifies 28 gene transcripts out of 31 gene transcripts (i.e., greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions.

Applicants also submit herewith a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 2). Dr. Scott is an independent expert in the field of molecular diagnostics, with over 15 years experience. He is the author of over 40 scientific publications in the fields of protein biology, gene discovery, and cancer, and is inventor on several issued patents. His curriculum vitae is attached to the declaration. In paragraph 10 of his declaration, Dr. Scott states:

> One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels. *Scott Declaration* at ¶10 (emphasis added).

Applicants submit the opinion of yet another expert in the field that changes in mRNA level for a particular protein in a given tissue generally lead to a corresponding change in the level of the encoded protein. Importantly, Dr. Scott also states that, contrary to the contentions of the PTO, diagnostic markers can be identified "without the need to directly measure individual protein expression levels." This opinion is supported by Dr. Scott's extensive experience in the field, as well as the fact that an entire industry has developed around technology used to assess differential mRNA expression. As stated previously, there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels.

The case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. *In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.C.P.A. 1976) and *In re Piasecki,* 745 F.2d. 1015, 226 USPQ 881 (Fed. Cir. 1985). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner." *Id.* at 1583. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Part IIB, 66 Fed. Reg. 1098 (2001).

In summary, Applicants have submitted herewith two additional expert Declarations in addition to the declarations and over 115 references already of record, which support Applicants' asserted utility, either directly or indirectly. This evidence supports the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein. As Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions. However, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt. *See M.P.E.P.* at § 2107.02, part VII (2004). Therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility. Applicants submit that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants' asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true." *Id.*

The PTO's Position is Inconsistent with the Utility Guidelines and the Courts

In response to Applicants' evidence and arguments, the PTO takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed antibodies – specifically, direct evidence of differential expression of PRO994 polypeptide in tumor and normal tissue. Applicants submit that this requirement is inconsistent with the Utility Guidelines and the courts.

In response to the over 100 supporting references submitted in Applicants' previous response, the PTO makes the following argument:

> ...the Examiner maintains that Applicants' measurement of an increase of PRO994 mRNA does not provide a specific and substantial utility for the encoded protein. Applicant has submitted several references showing that in some cases, there is a correlation between mRNA expression and the expression of the encoded protein. The PTO has provided many references that indicate that this correlation is hardly universal and that underscore the conclusion that it is improper to correlate nucleic acid and protein expression data, particularly in the case of cancerous tissue samples. Thus the state of the art of mRNA-protein expression correlations is quite clearly unpredictable. In some cases, there may be correlations, but in other cases there are not likely to be correlations. No clear generalizations can be made as to whether the expression of a protein product will change when the expression of a nucleic acid that encodes said protein changes.

> Applicant's assertion that it is more likely than not true that there is such a correlation is not borne out by the evidence of record. *Office Action* at 7-8.

Thus, the PTO implies the following argument: (1) the evidence of record demonstrates that there are exceptions to the general rule that increased mRNA levels correspond to increased levels of the encoded polypeptide; (2) because such exceptions exist, it is mandatory that specific data of differential PRO994 polypeptide expression in stomach and rectal tumors as compared to their normal tissue counterparts be disclosed; and (3) since such is not disclosed, the claimed PRO994 polypeptides have no substantial utility.

Adopting the PTO's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto. Thus, the PTO chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility. This heightened utility requirement is inconsistent with the Utility Guidelines and the courts. There is no requirement that utility be dispositively proven:

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965) ... Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* 2107.02 VII (emphasis in original).

There is no requirement that only direct evidence of utility is sufficient to establish utility. Instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101. *Nelson v. Bowler*, 626 F.2d 853, 856. Furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility. Instead, there only need be a reasonable correlation between the indirect evidence and the asserted utility. *Id.* at 857, *Cross v. Iizuka*, 753 F.2d 1040, 1050-1051. The indirect evidence need not absolutely prove the asserted utility. All that is required is that the tests be reasonably indicative of the asserted utility. In other words, there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a reasonable probability, that the novel compound will possess the asserted utility. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564.

In the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide). Insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. §101 as provided by the guidance of the Utility Guidelines and the courts.

In conclusion, the PTO's heightened requirement for establishing utility of the presently claimed polypeptides is contrary to the Utility Guidelines and the courts: it is sufficient to present evidence of differential mRNA expression since it is understood in the art that differential mRNA expression is reasonably linked to differential polypeptide expression. As discussed above, even if the PTO has presented evidence that changes in mRNA expression is not always correlated with changes in protein expression, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level typically lead to corresponding changes in protein level. As such, Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO994 mRNA is differentially expressed in stomach and rectal tumors as compared to their normal tissue counterparts, the PRO994 polypeptide will likewise be differentially expressed in stomach and rectal tumors. Accordingly, when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO994 polypeptide establishes the claimed polypeptides useful as diagnostic tools for cancer, particularly stomach and rectal cancer. In view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejections under 35 U.S.C. § 112, first paragraph – Enablement

The PTO also maintains its rejection of the pending claims under 35 U.S.C. § 112, first paragraph. Specifically, the PTO asserts that because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed

polypeptides. The PTO's rejection is based on lack of utility, which Applicants have fully addressed above. For the reasons set forth in the section addressing the rejection under 35 U.S.C. § 101, Applicants respectfully request that the PTO reconsider and withdraw the rejection of Claims 6-7, 9 and 11-17 under 35 U.S.C. § 112, first paragraph.

The PTO goes on to state that even if utility were found for PRO994, enablement would still not be commensurate in scope with Claims 6, 9 and 12-17 because the specification does not reasonably provide enablement for fragments or variants 95% or 99% identical to SEQ ID NO:48 which can be used to make antibodies to detect the full-length protein. *Office Action* at 8.

Applicants submit that Claims 6, 9, and 11-13 are fully enabled. The scope of these claims is narrow; they do not recite percent amino acid sequence identity as a limitation. These claims are directed to peptides of the disclosed sequence, specific fragments made up of amino acids 32-49 and 111-190 of the discosed sequence, the specific sequence deposited with the ATCC, and fusion proteins thereof which would be optimal, for example, in making antibodies. Because SEQ ID NO:48, the specific fragments claimed, and ATCC deposit 203018 are all explicitly disclosed in the specification, no experimentation of any kind is required to make the claimed polypeptides. One of skill in the art would clearly be able to use these polypeptides to make antibodies which are specific to any of these polypeptides, such that the level of expression of these polypeptides could be assessed in stomach and rectal tissue. For the reasons discussed at length above, Appellants believe that differential expression of the PRO994 mRNA in certain tumors provides the claimed polypeptides with a substantial and specific utility. Therefore, Claims 6, 9 and 12-13 are enabled.

As for Claims 14-17, the standard for determining whether the specification meets the enablement requirement is to be evaluated based on whether or not the experimentation needed for one skilled in the art to practice the invention would be undue. *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916); *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); *M.P.E.P.* § 2164.01. Applicants submit that in view of the requirements of enablement under 35 U.S.C. §112, first paragraph, the PTO has failed to establish a *prima facie* basis for rejecting Claims 14-17 as lacking enablement. The PTO's statements fail to establish a reasonable basis to question the enablement provided for the claimed invention. *See M.P.E.P.* § 2164.04.

The M.P.E.P. states that "if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention." *M.P.E.P.* § 2164.01(c) (emphasis added). As described below, the specification adequately discloses how to make and use the polypeptides of Claims 14-17. The subject matter of Claims 14-17 relates to isolated polypeptides with at least 95% identity to the disclosed polypeptides wherein the isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO:48 in stomach or rectum tissue samples.

The specification teaches in detail how to make the claimed polypeptides, including variants thereof, and antibodies which specifically bind PRO994. *See, e.g.*, ¶¶ [0283]-[0315]; [0256]-[0271]; [0361]-[0379]; and Examples 6-10 (¶¶ [0453]-[0499]). In addition, the specification discloses that antibodies to claimed polypeptides can be used in diagnostic assays to detect the expression of PRO994 in specific types of tissue. *See e.g., Specification* at [0407].

Thus, there is significant guidance on how to make and use the claimed polypeptides. In addition, as the disclosure and references cited in the specification make clear, the production of polypeptides, polypeptide variants, and specific antibodies is a predictable and well established aspect of the biological sciences. *See, e.g., In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) (reversing the Board's decision of non-enablement and holding that as of 1980, undue experimentation was not required to make high-affinity monoclonal antibodies to a target peptide); *Sutcliffe et al.,* Science (1983) 219:660-666 at 661-662 (teaching that "by following simple rules, one can in general select peptides that will elicit antibodies reactive with intact proteins").

In conclusion, the PTO's rejection based on lack of utility has been addressed above, and the PTO has otherwise failed to meet its burden to establish a reasonable basis to question the enablement provided for the claimed invention. Given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, first paragraph – Written Description

The PTO maintains the rejection of Claims 14-17 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement for the reasons set forth in the previous

Office Actions. Briefly, the PTO asserts that the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred. In addition, the PTO asserts that the claims are not analogous to Example 14 of the written description training materials. *Office Action* at 10.

Applicants maintain that pending Claims 14-17 are analogous to the claims discussed in Example 14 of the written description training materials available on the PTO's website. In Example 14, the written description requirement was found to be satisfied for claims directed to polypeptides with 95% homology to a disclosed sequence that also possess a recited catalytic activity, where procedures for making variant proteins were routine in the art and the specification provided an assay for detecting the recited catalytic activity of the protein. This disclosure satisfies the written description requirement even though the applicant had disclosed only a single species and had not made any variants. The Guidelines state that "[t]he single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity."

Like Example 14, Claims 14-17 have very high sequence homology to the disclosed sequence and must share an epitope sufficient to generate antibodies which specifically detect the polypeptide of SEQ ID NO:48 in stomach or rectum tissue samples. As in Example 14, at the time of the effective filing date of the instant application, it was well known in the art how to make polypeptides with at least 95% amino acid sequence identity to the disclosed sequences. *See, e.g., Specification* at ¶¶ [0256]-[0271]. In addition, the specification discloses in detail how to make antibodies which specifically detect a particular PRO polypeptide, and how to use them to detect the PRO polypeptide in a particular tissue. *See, e.g., Specification* ¶¶ [0363]-[0379], [0407], and [0493]-[0499]. Like a particular catalytic activity, the function of being useful to produce an antibody specific to SEQ ID NO:48 is directly related to the structure of the claimed polypeptides. Thus, like Example 14, the genus of polypeptides that have at least 95% amino acid sequence identity to the disclosed sequences and possess the described functional activity are adequately described.

Thus, there is significant guidance on how to make and use the claimed polypeptides. In addition, as the disclosure and references cited in the specification make clear, the production of polypeptides, polypeptide variants, and specific antibodies is a predictable and well established aspect of the biological sciences. *See, e.g., In re Wands*, 858 F.2d 731, 8 U.S.P.Q. 2d 1400 (Fed. Cir. 1988) (reversing the Board's decision of non-enablement and holding that as of 1980, undue experimentation was not required to make high-affinity monoclonal antibodies to a target peptide); *Sutcliffe et al.,* Science (1983) 219:660-666 at 661-662 (teaching that "by following simple rules, one can in general select peptides that will elicit antibodies reactive with intact proteins") (attached as Exhibit 3).

As for the PTO's statement that "the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred...," the basic premise that a large genus can not be adequately described by a single species is simply wrong. In a recent Federal Circuit decision, *In re Wallach*, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004), the Court stated:

> [W]e agree with Appellants that the state of the art has developed such that the complete amino acid sequence of a protein may put one in possession of the genus of DNA sequences encoding it, and that one of ordinary skill in the art at the time the '129 application was filed may have therefore been in possession of the entire genus of DNA sequences that can encode the disclosed partial protein sequence, even if individual species within that genus might not have been described or rendered obvious. ... A claim to the genus of DNA molecules complementary to the RNA having the sequences encompassed by that formula, even if defined only in terms of the protein sequence that the DNA molecules encode, while containing a large number of species, is definite in scope and provides the public notice required of patent applicants.
>
> ***
>
> Moreover, we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it. *Id.* (emphasis added).

The Court did not require the applicants in *Wallach* to actually make or individually describe all of the vast number of sequences which encode the disclosed sequence. This is in

spite of the fact that only a single sequence was disclosed, and the encompassed genus was enormous due to codon degeneracy in the genetic code – even the most skilled artisan could not individually envision the detailed chemical structure of the nucleic acids encompassed by the claimed genus. The Court reasoned that because it is routine to convert between amino acid sequences to nucleic acid sequences, disclosure of a single amino acid sequence was sufficient to place the applicants in possession of the enormous genus of nucleic acids which could encode the sequence.

The facts in *Wallach* are very similar to the instant case. Here, Applicants have disclosed SEQ ID NO:48, and claim polypeptides which are at least 95% identical to it and have the functional limitation of the ability to generate antibodies which can be used to specifically detect SEQ ID NO:48 in stomach and rectum tissue samples. As discussed above, it is routine in the art to create polypeptides which have at least 95% sequence identity to SEQ ID NO:48 – it is just as predictable and easy as creating all of the nucleic acids which encode a particular amino acid sequence. Similarly, it is well within the knowledge of those skilled in the art how to determine which polypeptides can be used to make the recited antibodies. The predictability of this structure/function combination is sufficient to place the claimed subject matter in the possession of the Applicants, and thus the claimed polypeptides are adequately described. The *Wallach* opinion makes clear that there is no need to literally describe more than a single species to adequately describe a large genus where one of skill in the art recognizes that the disclosed species puts the applicant in possession of the claimed genus.

In conclusion, Applicants submit that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:48, by specifying a high level of amino acid sequence identity, and by describing how to make antibodies to the disclosed sequence, all of which result in a lack of substantial variability in the species falling within the scope of the instant claims. Applicants submit that this disclosure would allow one of skill in the art to "recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus." Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

Rejection under 35 U.S.C. §112, first paragraph – New Matter

The PTO reject Claims 6, 9 and 12-17 under 35 U.S.C. § 112, first paragraph, as failing to satisfy the written description requirement. The PTO asserts that the claims each encompass polypeptides comprising amino acid sequences selected from residues 32-49 and 111-190 of SEQ ID NO:48, or polypeptides at least 95% identical thereto, or chimeric proteins comprising the same. The PTO says there is no support for proteins comprising these regions in the specification as originally filed. *Office Action* at 13.

Applicants maintain that they have satisfied the written description requirement for the pending claims based on the actual reduction to practice of SEQ ID NO:48, by specifying a high level of amino acid sequence identity, and by describing how to make and use antibodies to the disclosed sequence, for example in paragraph [0014], which states "[a]nother embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, *for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody*, paragraph [0288], paragraph [0313], and in paragraphs [0362] – [0349]. Taken together, it is clear that there is a lack of substantial variability in the species falling within the scope of the instant claims. For the reasons provided in the above discussion regarding the written description requirement, Applicants maintain that the specification adequately describes the claimed polypeptides. Accordingly, the claims do not contain new matter.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Appl. No. : **10/063,553**
Filed : **May 2, 2002**

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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